

**REMARKS**

Applicants have substituted into the present specification a new paper copy Sequence Listing section according to 37 C.F.R. §1.821(c) as new pages 1-8. Furthermore, attached hereto is a 3 1/2" disk containing the "Sequence Listing" in computer readable form in accordance with 37 C.F.R. §1.821(e).

Applicants have amended the specification to insert SEQ ID Nos, as supported in the present specification.

The following statement is provided to meet the requirements of 37 C.F.R. §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sheets of the sequence listing are believed to be supported in the application as filed and that the substitute sheets of the sequence listing are not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is the same as the attached substitute paper copy of the sequence listing.

Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the

origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current

amendment. The attached page is captioned "Version with markings to show changes made".

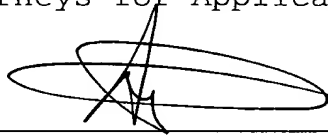
Applicants submit that the present application contains patentable subject matter and therefore urge the examiner to pass the case to issuance.

If the examiner has any questions or comments concerning the above described application, the examiner is urged to contact the undersigned at the phone number below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning at line 7 of page 8 has been amended as follows:

(vi) A chimeric sIL-6R/IL-6 protein, being the herein designated sIL-6R $\delta$ Val/L/IL-6 having a 13 amino acid peptide linker of sequence E-F-G-A-G-L-V-L-G-G-Q-F-M (SEQ ID NO:1) between the C-terminal Val-356 of sIL-6R and the N-terminal Pro-29 of IL-6R, said chimeric protein having the sequence set forth in Fig. 3 wherein the tripeptide of sequence E-F-M between positions 357-359 of Fig. 3 is replaced by said 13 amino acid peptide sequence.

The paragraph beginning at line 19 of page 12 has been amended as follows:

Figure 1 (A, B) depicts a schematic representation of the various vectors, reagents and process steps used in the construction of the chimeric DNA molecule encoding a chimeric protein in which is conserved the structure of the natural form of sIL-6R ending at the Val 356 residue followed by the sequence of the natural, mature, processed form of IL-6, as detailed in Example 1. In Fig. 1A, the reverse primer is complementary to SEQ ID NO:9 and in Fig. 1B, the EcoRI enzyme recognition site and the strand of the IL-6 cDNA sequence is presented as SEQ ID NO:10.

The paragraph beginning at line 7 of page 13 has been amended as follows:

Figure 3 depicts the amino acid sequence (one-letter code) (SEQ ID NO:7) of the sIL-6R $\delta$ Val/IL-6 chimera in which is shown the different domains of the molecule, including the N-terminal signal peptide (line on top of sequence), the immunoglobulin-like (Ig-like) domain, the cytokine receptor N-domain (underlined), the cytokine C-domain (line on top of sequence) and the receptor pre-membrane region (the region between the C-domain and the transmembranal domain), all of the sIL-6R part of the chimera; as well as the mature IL-6 moiety (underlined below) of the chimera, as described in Examples 1 and 2;

The paragraph beginning at line 1 of page 15 has been amended as follows:

Figure 11 depicts the amino acid sequence (one letter code) (SEQ ID NO:8) of the IL-6-sIL-6R $\delta$ Val chimera 3e, the linker being underlined; and

The paragraph beginning at line 10 of page 30 has been amended as follows:

As indicated above, an advantageous characteristic of the sIL-6R $\delta$ Val/IL-6 construct is that it is essentially the fusion of the natural form of sIL-6R and of the natural form of IL-6 as they exist in the human body, and without extraneous polypeptide sequences. However, the conservation of the EcoRI site in the sIL-6R $\delta$ Val/IL-6 construct (Figure 1) allows to easily introduce linker polypeptide segments between the sIL-6R and the IL-6 moieties. One such construct with the

13-amino acid linker sequence Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met (SEQ ID NO:1) introduced between Val-356 of sIL-6R and Pro-29 of IL-6, was also constructed (sIL-6RδVal/L/IL-6).

The paragraph beginning at line 1 of page 41 has been amended as follows:

SpeI                      SmaI                      BamH1  
5' CT AGT GGG CCC GGG GTG GCG GG (SEQ ID NO:2)  
A CCC GGG CCC CAC CGC CCC TAG 5' (SEQ ID NO:12)

The paragraph beginning at line 19 of page 41 has been amended as follows:

SmaI  
5' GAT CCG GGC GGC GGG GGA GGG GGG CCC GGG C[NcoI] (SEQ ID NO:5)  
[BamH1] GC CCG CCG CCC CCT CCT CCC GGG CCC GGT AC 5'  
(SEQ ID NO:511)

In the claims:

Claims 5 and 7 have been amended as follows:

5. (Amended). A chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to claim 2, wherein said linker is a peptide of 13 amino acid residues of sequence E-F-G-A-G-L-V-L-G-G-Q-F-M (Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met) (SEQ ID NO:1).

7. (Amended). A chimeric sIL-6R/IL-6 protein according to claim 1, being the herein designated sIL-6R $\delta$ Val/L/IL-6 having a 13 amino acid peptide linker of sequence E-F-G-A-G-L-V-L-G-G-Q-F-M (SEQ ID NO:1) between the C-terminal Val-356 of sIL-6R and the N-terminal Pro-29 of IL-6, said chimeric protein having the sequence set forth in Fig. 3 wherein the tripeptide of sequence E-F-M between positions 357-359 of Fig. 3 is replaced by said 13 amino acid peptide sequence.